In addition, Applicants submit concurrently herewith to BOX SEQUENCE a computer-readable form (diskette) of the substitute Sequence Listing submitted herewith which is identical in substance to the paper copy of the substitute Sequence Listing on substitute pages 1-176 submitted herewith.

Applicants submit herewith a **"Version with Markings to Show Changes Made,"** which indicates the specific amendments made to the specification and the claims. For the Examiner's convenience, the pending claims are set forth in Appendix A. *No new matter has been added.* Applicant hereby reserves the right to pursue the subject matter of the claims as originally filed in this or a separate application(s).

CONCLUSION

In view of the amendments and remarks set forth above, it is respectfully submitted that this application is in condition for allowance. If the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Respectfully submitted,

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"Version with Markings to Show Changes Made"

Pages 1-175 of the Sequence Listing have been deleted and replaced with the Substitute Sequence Listing, pages 1-176, filed herewith.

The paragraph beginning at page 20, line 2, has been amended as follows:

The present invention is based, at least in part, on the discovery of novel molecules, referred to herein as MP nucleic acid and protein molecules (see Table 1), which play a role in or function in one or more cellular metabolic pathways. In one embodiment, the MP molecules catalyze an enzymatic reaction involving one or more amino acid, *e.g.*, lysine or methionine, vitamin, cofactor, nutraceutical, nucleotide, nucleoside, or trehalose metabolic pathways. In a preferred embodiment, the activity of one or more MP molecules of the present invention, alone or in combination with molecules involved in the same or different metabolic pathway (*e.g.*, methionine or lysine metabolism), in one or more *C. glutamicum* metabolic pathways for amino acids, vitamins, cofactors, nutraceuticals, nucleotides, nucleosides or trehalose has an impact on the production of a desired fine chemical by this organism. In a particularly preferred embodiment, the MP molecules of the invention are modulated in activity, such that the *C. glutamicum* metabolic pathways in which the MP proteins of the invention are involved are modulated in efficiency or output, which either directly or indirectly modulates the production or efficiency of production of a desired fine chemical by *C. glutamicum*. In a preferred embodiment, the fine chemical is an amino acid, *e.g.*, lysine or methionine. In another preferred embodiment, the MP molecules are metZ, ~~metY~~met C, and/or RXA00657 (see Table 1).

The paragraph beginning at page 26, line 18, has been amended as follows:

Also listed on Table 1 are the *metZ* (or *metY*) and *metC* genes (designated as SEQ ID NO:1 and SEQ ID NO:3, respectively. The corresponding amino acid sequence encoded by the *metZ* and *metC* genes are designated as SEQ ID NO:2 and SEQ ID NO:~~5~~ 4, respectively.

The paragraph beginning at page 79, line 19, has been amended as follows:

Transformation of a bacterial strain such as *Corynebacterium glutamicum* strain (ATCC 13286) was performed with a plasmid pB containing the aforementioned DNA regions of RXA00657 (SEQ ID NO.:6) and in another case with the vector pB (SEQ ID NO.:125) carrying no additional insertion of nucleic acids.

In the Claims:

Claims 1, 4, 25, 26, 27, 35, 38, 39, and 40 have been amended as follows:

1. (Amended) ~~1.~~ An isolated nucleic acid molecule from *Corynebacterium glutamicum* encoding a metabolic pathway protein selected from the group consisting of a nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:5.

4. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence which is at least 50% homologous to a nucleotide sequence set forth in SEQ ID NO:~~6~~ 5, or a complement thereof.

25. (Amended) The isolated polypeptide of claim ~~23~~ 24, further comprising heterologous amino acid sequences.

26. (Amended) An isolated polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 50% homologous to a nucleotide sequence set forth in SEQ ID NO:5, or a complement thereof.

27. (Amended) An isolated polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 65% homologous to a nucleotide sequence set forth in SEQ ID NO:1, or a complement thereof.

35. (Amended) The method of claim ~~27~~ 28, wherein said cell is selected from the group consisting of: *Corynebacterium glutamicum, Corynebacterium herculis, Corynebacterium, lilium, Corynebacterium acetoacidophilum, Corynebacterium acetoglutamicum, Corynebacterium acetophilum, Corynebacterium ammoniagenes, Corynebacterium fujiokense, Corynebacterium nitrilophilus, Brevibacterium ammoniagenes, Brevibacterium butanicum, Brevibacterium divaricatum, Brevibacterium flavum, Brevibacterium healii, Brevibacterium ketoglutamicum, Brevibacterium ketosoreductum, Brevibacterium lactofermentum, Brevibacterium linens, Brevibacterium paraffinolyticum,* and those strains set forth in Table 3.

38. (Amended) A method for producing a fine chemical, comprising culturing a cell whose genomic DNA has been altered by the inclusion of a nucleic acid molecule of any one of claims 1-6, alone or in combination with one or more metabolic pathway nucleic acid molecules.

39. (Amended) The method of claim ~~36~~ 38, wherein the metabolic pathway nucleic acid molecule is selected from the group consisting of *metZ*, *metC*, *metB*, *metA*, *metE*, *metH*, *hom*, *asd*, *lysC*, *lysC /ask*, rxa00657, *dapA*, *dapB*, *dapC*, *dapD/argD*, *dapE*, *dapF*, *lysA*, *ddh*, *lysE*, *lysG*, *lysR*, *hsk*, *ppc*, *pycA*, *accD*, *accA*, *accB*, *accC*, *gpdh* genes encoding glucose-6-

phophate-dehydrogenase, *opcA*, *pgdh*, *ta*, *tk*, *pgl*, *rlpe*, *rpe* or any combination of the above-mentioned genes.

40. (Amended) The method of claim ~~35 or 36~~ 38, wherein said metabolic pathway is methionine or lysine metabolism.

Appendix A

1. (Amended) An isolated nucleic acid molecule from *Corynebacterium glutamicum* encoding a metabolic pathway protein selected from the group consisting of a nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:5.

2. The isolated nucleic acid molecule of claim 1, wherein said metabolic pathway protein is involved in the metabolism of an amino acid.

3. An isolated nucleic acid molecule which encodes a naturally occurring allelic variant of a polypeptide selected from the group of amino acid sequences consisting of those sequences set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:6.

4. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence which is at least 50% homologous to a nucleotide sequence set forth in SEQ ID NO:5, or a complement thereof.

5. An isolated nucleic acid molecule comprising a nucleotide sequence which is at least 65% homologous to a nucleotide sequence set forth in SEQ ID NO:1, or a complement thereof.

6. An isolated nucleic acid molecule comprising a fragment of at least 15 nucleotides of a nucleic acid comprising a nucleotide sequence selected from the group consisting of those sequences set forth set forth in SEQ ID NO:1, SEQ ID NO:3, or SEQ ID NO:5.

7. An isolated nucleic acid molecule which hybridizes to the nucleic acid molecule of any one of claims 1-6 under stringent conditions.

8. An isolated nucleic acid molecule comprising the nucleic acid molecule of claim 1, or a portion thereof, and a nucleotide sequence encoding a heterologous polypeptide.

9. A vector comprising the nucleic acid molecule of claim 1.

10. The vector of claim 9, further comprising one or more metabolic pathway nucleic acid molecules.

11. The vector of claim 9 or 10, which is an expression vector.

12. A host cell transfected with the expression vector of claim 9 or 10.

13. The vector of claim 10, wherein the second metabolic pathway nucleic acid molecule is selected from the group consisting of a nucleic acid molecule comprising the nucleotide sequence set forth in the odd-numbered sequences listed in Table 1, excluding any F-designated nucleic acid molecules.

14. The host cell of claim 12, wherein said cell is a microorganism.

15. The host cell of claim 12, wherein said cell belongs to the genus *Corynebacterium* or *Brevibacterium*.

16. The host cell of claim 12, wherein the expression of said nucleic acid molecules results in the modulation in production of a fine chemical from said cell.

17. The host cell of claim 16, wherein said fine chemical is an amino acid.

18. The host cell of claim 17, wherein said amino acid is methionine or lysine.

19. A method of producing a polypeptide comprising culturing the host cell of claim 12 in an appropriate culture medium to, thereby, produce the polypeptide.

20. An isolated metabolic pathway polypeptide from *Corynebacterium glutamicum*, or a portion thereof.

21. The protein of claim 20, wherein said polypeptide is selected from the group of metabolic pathway proteins which participate in the metabolism of an amino acid.

22. The protein of claim 21, wherein said amino acid is methionine or lysine.

23. An isolated nucleic acid molecule from *Corynebacterium glutamicum* which encodes a metabolic pathway protein comprising the amino acid sequence set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:6.

24. An isolated polypeptide comprising a naturally occurring allelic variant of a polypeptide comprising an amino acid sequence selected from the group consisting of those sequences set forth in SEQ ID NO:2, SEQ ID NO:4, or SEQ ID NO:6.

25. (Amended) The isolated polypeptide of claim 24, further comprising heterologous amino acid sequences.

26. (Amended) An isolated polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 50% homologous to a nucleotide sequence set forth in SEQ ID NO:5, or a complement thereof.

27. (Amended) An isolated polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 65% homologous to a nucleotide sequence set forth in SEQ ID NO:1, or a complement thereof.

28. A method for producing a fine chemical, comprising culturing a cell containing a vector of claim 9 or 10, such that the fine chemical is produced.

29. The method of claim 28, wherein said cell is cultured in the presence of a sulfur source.

30. The method of claim 28, wherein said method further comprises the step of recovering the fine chemical from said culture.

31. The method of claim 28, wherein said fine chemical is an amino acid.

32. The method of claim 31, wherein said amino acid is methionine or lysine.

33. The method of claim 28, wherein said method further comprises the step of transfecting said cell with the vector of claim 9 or 10, to result in a cell containing said vector.

34. The method of claim 28, wherein said cell belongs to the genus *Corynebacterium* or *Brevibacterium*.

35. (Amended) The method of claim 28, wherein said cell is selected from the group consisting of: *Corynebacterium glutamicum, Corynebacterium herculis, Corynebacterium, lilium, Corynebacterium acetoacidophilum, Corynebacterium acetoglutamicum, Corynebacterium acetophilum, Corynebacterium ammoniagenes, Corynebacterium fujiokense, Corynebacterium nitrilophilus, Brevibacterium ammoniagenes, Brevibacterium butanicum, Brevibacterium divaricatum, Brevibacterium flavum, Brevibacterium healii, Brevibacterium ketoglutamicum, Brevibacterium ketosoreductum, Brevibacterium lactofermentum, Brevibacterium linens, Brevibacterium paraffinolyticum,* and those strains set forth in Table 3.

36. A method for producing a fine chemical, comprising culturing a cell whose genomic DNA has been altered by the inclusion of a nucleic acid molecule of any one of claims 1-6.

37. A method for producing a fine chemical, comprising culturing a cell whose genomic DNA has been altered by the inclusion of a nucleic acid molecule of any one of claims 1-6, alone or in combination with another metabolic pathway nucleic acid selected from the group consisting of a nucleic acid molecule comprising the nucleotide sequence set forth in the odd-numbered sequences listed in Table 1, excluding any F-designated nucleic acid molecules.

38. (Amended) A method for producing a fine chemical, comprising culturing a cell whose genomic DNA has been altered by the inclusion of a nucleic acid molecule of any one of claims 1-6, alone or in combination with one or more metabolic pathway nucleic acid molecules.

39. (Amended) The method of claim 38, wherein the metabolic pathway nucleic acid molecule is selected from the group consisting of *metZ*, *metC*, *metB*, *metA*, *metE*, *metH*, *hom*,

asd, *lysC*, *lysC /ask*, rxa00657, *dapA*, *dapB*, *dapC*, *dapD/argD*, *dapE*, *dapF*, *lysA*, *ddh*, *lysE*, *lysG*, *lysR*, *hsk*, *ppc*, *pycA*, *accD*, *accA*, *accB*, *accC*, *gpdh* genes encoding glucose-6-phophate-dehydrogenase, *opcA*, *pgdh*, *ta*, *tk*, *pgl*, *rlpe*, *rpe* or any combination of the above-mentioned genes.

40. (Amended) The method of claim 38, wherein said metabolic pathway is methionine or lysine metabolism.

41. A method of modulating the yield of a fine chemical from a cell comprising, introducing one or more metabolic pathway genes into a cell, thereby modulating the yield of a fine chemical.

42. The method of claim 41, wherein said metabolic pathway gene or genes are integrated into the chromosome of the cell.

43. The method of claim 41, wherein said metabolic pathway gene or genes are maintained on a plasmid.

44. The method of claim 41, wherein said fine chemical is an amino acid.

45. The method of claim 44, wherein said amino acid is methionine or lysine.

46. The method of claim 41, wherein said metabolic pathway gene or genes are selected from the group consisting of the nucleic acid molecule of any one of claims 1-6.

47. The method of claim 41, wherein the nucleotide sequence of said metabolic pathway gene or genes has been mutated to increase yield of a fine chemical.